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# **An intraocular pressure polygenic risk score stratifies multiple primary open angle glaucoma parameters including treatment intensity**

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**Running head:** POAG phenotype stratified by an IOP polygenic risk score

**Abbreviations/Acronyms:**

IOP: intraocular pressure; POAG: primary open angle glaucoma; PRS: polygenic risk score; ANZRAG: Australian and New Zealand Registry of Advanced Glaucoma; SD: standard deviation; MYOC: myocilin; OPTN: optineurin; TBK1: TANK-binding kinase 1; CI: confidence interval; GWAS: genome wide association study; SNP: single nucleotide polymorphism; OR: odds ratio; MD: mean deviation; VCDR: vertical cup-to-disc ratio; PROGRESSA: Progression Risk Of Glaucoma; RElevant SNPs with Significant Association; SLT: selective laser trabeculoplasty; IGGC: International Glaucoma Genetics Consortium.

## 58 **Abstract**

59 **Objective:** To examine the combined effects of common genetic variants associated with  
60 intraocular pressure (IOP) on primary open angle glaucoma (POAG) phenotype using a  
61 polygenic risk score (PRS) stratification.

62 **Design:** Cross-sectional study.

63 **Participants:** For the primary analysis, we examined the glaucoma phenotype of 2,154 POAG  
64 patients enrolled in the Australian and New Zealand Registry of Advanced Glaucoma  
65 (ANZRAG) including cases recruited from the UK. For replication, we examined an  
66 independent cohort of 624 early POAG patients.

67 **Methods:** Using IOP genome-wide association study summary statistics, we developed a  
68 PRS derived solely from IOP associated variants and stratified POAG patients into three risk  
69 tiers. The lowest and highest quintiles of the score were set as the low and high risk groups  
70 respectively and the other quintiles as the intermediate risk group.

71 **Main Outcome Measures:** Clinical glaucoma phenotype including maximum recorded IOP,  
72 age of diagnosis, number of family members affected by glaucoma, cup-to-disc ratio, visual  
73 field mean deviation, and treatment intensity.

74 **Results:** There was a dose-response relationship between the IOP PRS and the maximum  
75 recorded IOP, with the high genetic risk group having a higher maximum IOP by 1.7 (SD 0.62)  
76 mmHg than the low genetic risk group ( $P = 0.006$ ). Compared to the low genetic risk group,  
77 the high genetic risk group had a younger age of diagnosis by 3.7 (1.0) years ( $P < 0.001$ ),  
78 more family members affected by 0.46 (0.11) members ( $P < 0.001$ ), and higher rates of  
79 incisional surgery (odds ratio 1.5; 95% confidence interval 1.1 - 2.0;  $P = 0.007$ ). There was no  
80 statistically significant difference in mean deviation. We further replicated the maximum IOP,

81 number of family members affected by glaucoma and treatment intensity (number of  
82 medications) results in the early POAG cohort ( $P \leq 0.01$ ).

83 **Conclusions**: The IOP polygenic risk score was positively correlated with maximum IOP,  
84 disease severity, need for surgery and number of family members. Genes acting via IOP  
85 mediated pathways, when considered in aggregate have clinically important and reproducible  
86 implications for glaucoma patients and their close family members.

Glaucoma refers to a group of progressive optic neuropathies with a characteristic pattern of retinal ganglion cell death and visual field loss.<sup>1</sup> Intraocular pressure (IOP) is currently the only proven modifiable risk factor for primary open angle glaucoma (POAG), in which the iridocorneal angle is open and there is no secondary cause of IOP elevation.<sup>2</sup> Despite this, elevated IOP is not essential for the diagnosis of POAG, nor is it effective for screening for glaucoma.<sup>1,3</sup> The current methods of IOP assessment are limited to the time of measurement and are a poor measure of an individual's IOP profile, maximum and fluctuations. Additional IOP measurements are more informative for glaucoma management as both diurnal and long-term IOP fluctuations have been reportedly associated with glaucoma progression.<sup>4,5</sup>

Glaucoma is highly heritable and several genes with a Mendelian pattern of inheritance have been associated with POAG.<sup>6</sup> Monogenic variants causing glaucoma are relatively rare but carry a high risk of developing the disease. Family-based genetic linkage analysis has identified three genes associated with Mendelian glaucoma; myocilin (*MYOC*), optineurin (*OPTN*) and TANK-binding kinase 1 (*TBK1*) genes.<sup>7-10</sup> Pathogenic variants in the *MYOC* gene account for 2-4% of adult-onset POAG.<sup>10</sup> The most common pathogenic variant in the *MYOC* gene in individuals of European ancestry (p.Gln368Ter) has a minor allele frequency of 0.13%, yet carries a significant risk of glaucoma with high IOP in those who carry it (in a population based setting odds ratio [OR] = 6.76 with 95% confidence interval [CI] of 4.05-11.29).<sup>11</sup> In family-based studies, the penetrance of p.Gln368Ter to manifest POAG is reported at approximately 80% by the seventh decade of life.<sup>11</sup>

IOP in the normal population is a polygenic trait, with recent large genome-wide association studies (GWAS) discovering more than one hundred common loci associated with IOP, accounting for 40% of the heritability.<sup>12-14</sup> Khawaja *et al.* reported that these single nucleotide polymorphisms (SNPs) explained 17% of IOP variance in an independent clinical study, and 9% in the UK biobank study which likely reflects the difference in IOP measurement methods.<sup>14</sup> In contrast to the aforementioned monogenic variants, each SNP contributes a very small

effect size. For instance, variants in or near the genes *TMCO1* and *CAV2*, two of the most strongly associated loci with IOP and glaucoma, are present in 10-15% of the population but account for a modest risk of glaucoma individually (OR 1.1 - 1.4).<sup>12-14</sup> However, the combined effects of these common SNPs significantly affect the observed clinical phenotype.<sup>12</sup>

To understand the impact of these common variants, we consider the total number of variants an individual is carrying multiplied by their effect size, to generate a weighted polygenic risk score (PRS).<sup>15</sup> A genetic risk stratification may then be done by calculating an aggregate score of all the SNPs an individual has associated with a trait. For instance, a person with the majority of the discovered IOP variants (a high IOP PRS) is hypothesised to have a higher IOP than someone who has only a few. The PRS model of risk prediction has been used to stratify individualised disease risk in several medical conditions such as coronary artery disease, atrial fibrillation and breast cancer.<sup>16-18</sup> Recently, a PRS derived from the known IOP variants has been reported to account for a higher risk of developing glaucoma;<sup>12</sup> however, the influence of the IOP PRS on a wider range of glaucoma-related phenotypes has not been described. In this study, we aimed to characterise the clinical features of glaucoma patients with a high burden of IOP associated variants in a large national Australian glaucoma registry along with ethnically similar cases from the UK.

## **Methods**

### **Study participants**

The study adhered to the tenets of the Declaration of Helsinki and followed the National Health and Medical Research Council statement of ethical conduct in research involving humans. Informed consent was obtained from all participants, and the study was approved by the Southern Adelaide Clinical Human Research Ethics Committee.

The study participants were enrolled in the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG).<sup>19</sup> The study includes both advanced and non-advanced glaucoma cases. Advanced glaucoma was defined by a Humphrey 24-2 visual field mean deviation (MD) < -15 dB in the worse eye, or loss of at least two of the central visual field points on the pattern deviation map.<sup>19</sup> Non-advanced glaucoma was defined by optic nerve head changes with corresponding visual field defects consistent with glaucoma, but not fitting the aforementioned criteria. The study sample included additional ethnically matched advanced glaucoma cases recruited from the UK (contributed by AJL, CEW and NAV). Only patients of European ancestry with POAG were included to utilise the currently published IOP SNPs. Patients with variants in the known POAG genes (*MYOC*, *OPTN* and *TBK1*) were excluded. The highest IOP measurement recorded with Goldmann applanation tonometry by an experienced clinician before treatment of either eye for each participant was recorded. High tension glaucoma was defined as a maximum recorded IOP > 21 mmHg. Other data recorded included age at diagnosis, vertical cup-to-disc ratio (VCDR), and glaucoma surgery. Family history was self-reported and recorded for affected relatives up to the fourth degree.

An independent cohort of early glaucoma patients enrolled in the Progression Risk Of Glaucoma; RElevant SNPs with Significant Association (PROGRESSA) study were then used for replication. Only participants with established perimetric glaucoma, defined by two consecutive reliable visual field examinations with Glaucoma Hemifield Test "Outside Normal Limits", pattern standard deviation <5%, or a cluster of 3 contiguous points depressed <5% in the pattern standard deviation map, at least one of which is <1%, were included. Data recorded included self-reported family history of glaucoma, maximum IOP recorded, VCDR, number of topical glaucoma medications and previous selective laser trabeculoplasty (SLT).



## **Polygenic risk score**

The IOP derived PRS was comprised of 146 statistically independent genome-wide-significant SNPs (P value threshold at  $5 \times 10^{-8}$  and LD-clumping at  $r^2 = 0.1$ ) as reported previously (Supplementary Table 1).<sup>12</sup> Briefly, SNPs influencing IOP were discovered by a GWAS of cornea-compensated IOP measured by Ocular Response Analyzer in participants of the UK Biobank study (N = 103,914).<sup>12,20</sup> This was meta-analysed with GWAS results from the International Glaucoma Genetics Consortium (IGGC, N = 29,578) using the inverse variance weighted method (METAL software).<sup>21</sup> A weighted PRS was then derived for each individual in the ANZRAG study cohort using PLINK (version 1.90 beta),<sup>22</sup> taking into account the effect size of each SNP using the UK Biobank GWAS summary statistics. None of the study participants in ANZRAG or PROGRESSA were part of the discovery cohort. A percentile score was then derived within the ANZRAG and the PROGRESSA cohorts. We classified patients into three risk groups; the top 20% of the genetic risk score were classified as the high risk group; the middle 60% as the intermediate risk group; and the bottom 20% as the low risk group. Genotyping was done in several phases on either Illumina Omni1M, OmniExpress or HumanCoreExome arrays (Illumina, San Diego, CA, USA) as described previously.<sup>12</sup>

## **Statistical analysis**

The Shapiro-Wilk test was used to assess for normality. Analysis of variance of continuous variables by PRS groups was done using Kruskal–Wallis test. Count and categorical variables were compared using Pearson's chi-squared test. For two-group comparisons, the Mann-Whitney U test was used. Logistic regression models were fitted for binary outcomes and negative binomial regression was used for count data (number of family members affected). All analysis was done using R (version 3.5.1, RCore Team, Austria).<sup>23</sup> The significance level (alpha) was set at 0.05.

## Results

A total of 2,154 eligible POAG patients from ANZRAG with mean age at recruitment of 77.4 (SD 13.2) years were included. The majority of the study cohort (N = 1,664; 77%) had advanced glaucoma as defined above. This included 381 cases recruited from the UK (N = 290 from Southampton and N = 91 Liverpool) who were ethnically matched to the rest of the cohort. A summary of the glaucoma phenotype across the three genetic risk groups is summarised in Table 1.

The high IOP genetic risk group had a significantly higher maximum IOP by 1.3 mmHg (95%CI: 0.32 - 2.7 mmHg;  $P = 5.5 \times 10^{-3}$ ) compared to the intermediate and low genetic risk groups. The maximum IOP was not statistically significantly different in the intermediate group relative to the low risk group (mean difference of 0.54 mmHg, 95% CI -1.5 - 0.47 mmHg;  $P = 0.08$ ). Similarly, the high genetic risk group was more likely to present as high tension glaucoma, defined by a maximum IOP above 21 mmHg (OR = 1.9; 95% CI 1.3 - 2.8;  $P = 7.9 \times 10^{-4}$  relative to the low-risk group). Further analysis by decile groups of the IOP PRS shows a continuous variant dose-response relationship between higher IOP PRS and maximum IOP, signifying the cumulative effects of the common IOP variants (Figure 1A).

The mean age of glaucoma diagnosis was significantly different across the genetic risk groups ( $P = 1.3 \times 10^{-4}$ ). The high genetic risk group were diagnosed with glaucoma on average 2.2 (SD 0.80) years earlier than the intermediate group ( $P = 5.5 \times 10^{-3}$ ) and 3.7 (SD 1.0) years than the low genetic risk group ( $2.4 \times 10^{-4}$ ). The high risk group were more likely to have family members affected by glaucoma relative to the low risk group (OR = 1.6, 95% CI 1.2 - 2.1.  $P = 1.1 \times 10^{-3}$ ). The number of self-reported family members affected by glaucoma was also higher in the high IOP PRS group compared to the intermediate (mean 0.29, SD 0.1,  $P = 5.2 \times 10^{-3}$ ) and low risk groups (mean 0.46, SD 0.11,  $P = 1.8 \times 10^{-4}$ ). Furthermore, there was a linear relationship between the IOP PRS and the number of family members affected by glaucoma which

highlights the importance of these variants and their impact on the development of glaucoma (Figure 1B).

There was no significant difference between the Humphrey visual field mean deviation between the IOP PRS groups ( $P = 0.18$ ). However, the high genetic risk group were more likely to require an incisional surgery for the management of their glaucoma relative to the intermediate and low risk groups ( $OR = 1.3$ , 95%  $CI = 1.0 - 1.6$ ;  $P = 0.049$  and  $OR = 1.5$ ; 95%  $CI = 1.1 - 2.0$ ;  $P = 7.9 \times 10^{-3}$  respectively). Further, the high IOP PRS group were more likely to require bilateral incisional surgeries than the intermediate and low risk groups ( $OR = 1.4$ , 95%  $CI = 1.0 - 1.8$ ;  $P = 0.02$ ).

For replication, we stratified an independent cohort of early perimetric POAG patients ( $N = 624$ ), with an average age of 69.5 (10) years, into three risk groups based on the same absolute numerical IOP PRS cut-off used above. There was a similar association of increasing maximum IOP, number of family members affected, and treatment intensity (Table 2 and Figure 2). The high risk group had more than twice as many family members affected as the low risk group, and were more likely to require more intensive medical therapy to control their disease ( $P \leq 0.01$ ).

## Discussion

Common genetic variants associated with both glaucoma and IOP have been identified via genome-wide association studies. Genetic risk score stratification can be used to estimate the combined effect size of these variants on the patient. In this study, glaucoma patients in the high IOP genetic risk group had a higher maximum (pre-treatment) IOP, younger age of glaucoma diagnosis, and were more likely to require incisional surgery to control their disease

than those in the intermediate or low IOP genetic risk groups. We have further replicated these results in an independent cohort of early glaucoma patients and observed a similar association with the higher genetic risk group requiring more intensive medical therapy for glaucoma management.

Interestingly, despite the clinically modest difference in the maximum IOP between the high and low IOP genetic risk groups (between 1-2 mmHg in two independent cohorts), we observed a stronger relationship in treatment intensity. In the ANZRAG cohort, the incisional surgery rate was 50% in the high genetic risk group compared to 38% in the low risk group. Similarly, in the early glaucoma cohort, 38% of the high genetic risk group required 2 or more medications or SLT for glaucoma management compared to 23% in the low genetic risk group. Thus, IOP genetic risk variants and stratification may offer further insight into an individual's chronic exposure to higher IOP than sporadic clinic measurements. Further, these risk variants confer increased risk of developing POAG in carriers,<sup>12</sup> thus patients with higher polygenic risk scores had significantly more family members affected by glaucoma.

Previous studies of common genetic variants in glaucoma have focused on individual SNPs only. *TMCO1* was one of the earliest reported genes to be associated with POAG in common variant studies, and remains one of the most strongly associated variants with IOP and POAG.<sup>12,14,24</sup> A variant in *TMCO1* gene is reportedly associated with conversion from ocular hypertension to glaucoma in non-Hispanic whites<sup>25</sup> In another study, individuals homozygous for a variant near *TMCO1* were reported to have a younger age of POAG onset.<sup>26</sup> However, the clinical utility of genetic risk scores is expanding due to the accelerated discovery of disease-associated loci as larger genome-wide association studies are conducted. While early studies on using genetic risk scores for POAG were limited,<sup>27,28</sup> Macgregor *et al.* have recently reported an IOP based genetic risk score accounting for a significant risk of developing glaucoma (OR = 5.6 in the highest decile of the score relative to the lowest).<sup>12</sup>

Conversely, the effects of Mendelian variants on glaucoma phenotype have been well described. Pathogenic variants in the *MYOC* gene are most commonly associated with high IOP and more advanced disease.<sup>29</sup> In contrast, duplications and triplications involving *TBK1* and missense variants in *OPTN* cause familial normal tension glaucoma, and are typically not found in high tension glaucoma.<sup>7–9</sup> While these genes are important in familial glaucoma and highly predictive of disease risk, they are a relatively rare cause of POAG in the general population. Thus, genetic risk stratification using common variants of IOP is more widely applicable to most POAG patients. Our results show that the cumulative effect of IOP-associated genetic variants may predict an individual's lifetime IOP exposure, and support the utility of genetic risk scores in POAG monitoring. Further, PRS risk stratification can be done before the clinical presentation of the disease, and therefore may be useful for identifying high-risk individuals for screening. To our knowledge, this is the first study to detail the clinical glaucoma phenotype based on the combined effect of common IOP variants.

This study has several strengths. We utilised the large UK Biobank cohort to derive a genetic risk score of corneal compensated IOP. Our study cohort was also independent allowing validation of the discovered variants. We have further replicated our findings in another independent POAG cohort with mild glaucoma allowing further generalisability across the glaucoma severity spectrum. Our study has also some limitations. Genetic risk scores are limited by the genetic pool of the discovery cohort. Our results are limited to the ethnicities of the European ancestry individuals of the UK Biobank study which matched our prediction target cohort. Validation is needed in other ethnicities. We have only used SNPs that reached genome-wide significance in the GWAS to calculate the PRS. While the inclusion of additional SNPs would include further low-impact susceptibility SNPs, it would also introduce further 'noise' to the PRS and may not improve risk stratification.<sup>30</sup>

In conclusion, our IOP PRS correlates with the maximum recorded IOP and glaucoma severity of POAG patients in a national glaucoma registry. Our result supports the clinical utility of PRS in POAG risk stratification.

#### **Acknowledgments:**

This work was conducted using the UK Biobank Resource (application number 25331) and publicly available data from the International Glaucoma Genetics Consortium.

#### **Figure legends:**

**Figure 1.** A continuous variant dose-response relationship between IOP PRS and (A) the maximum recorded IOP in the ANZRAG cohort ( $P = 1.9 \times 10^{-3}$  for linear model trend); (B) the mean number of family members affected by glaucoma ( $P = 1.3 \times 10^{-5}$  for negative binomial generalised linear model trend). The squares represent the mean values for each PRS decile group, and the error bars represent the 95% confidence interval of the mean. The grey line is the line of best fit with the 95% confidence interval lightly shaded around the line.

IOP: intraocular pressure; PRS: polygenic risk score.

**Figure 2.** Replication of the (A) maximum IOP recorded ( $P = 5.0 \times 10^{-4}$  for one-way analysis of variance) and (B) the number of family members affected by glaucoma ( $P = 1.0 \times 10^{-3}$  for one-way analysis of variance) in an independent cohort of early POAG patients ( $N = 624$ ). The squares represent the mean values for each PRS group, and the error bars represent the 95% confidence interval of the mean.

IOP: intraocular pressure; PRS: polygenic risk score; POAG: primary open angle glaucoma.

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Figure 1

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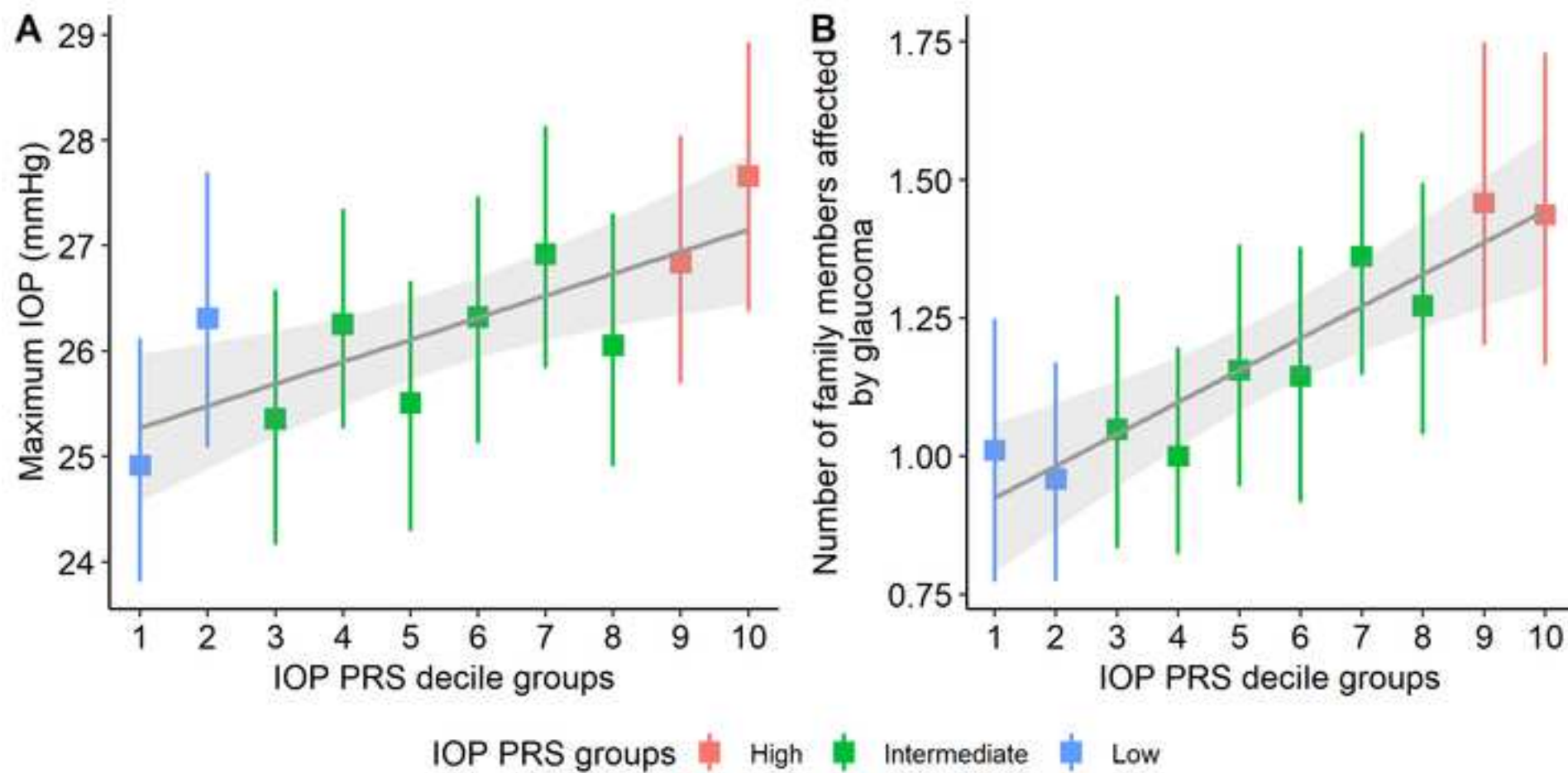
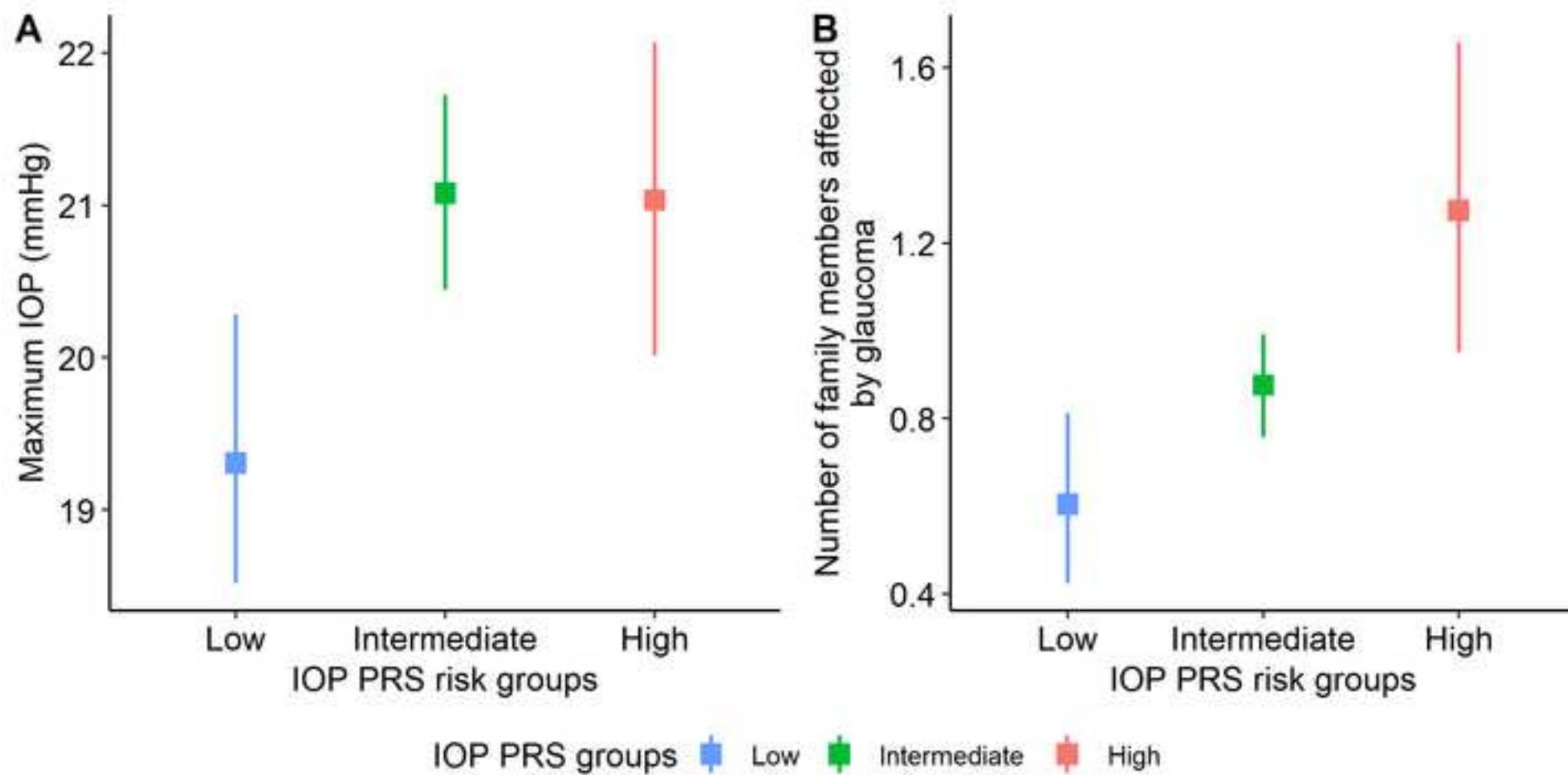


Figure 2

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**Table 1:** Summary of the glaucoma phenotype across genetic risk groups in ANZRAG

	Low	Intermediate	High	p
Number	410	1313	431	-
Gender, male (%)	192 (46.8)	622 (47.4)	185 (43.0)	0.3
HTG (%)	251 (74.3)	867 (79.1)	298 (84.7)	<b>0.003</b>
Age of diagnosis, years	62.90 (15.32)	61.39 (14.16)	59.16 (13.80)	<b>&lt;0.001</b>
Family members affected	0.99 (1.56)	1.16 (1.53)	1.45 (1.89)	<b>0.001</b>
Maximum recorded IOP, mmHg	25.54 (9.17)	26.08 (8.63)	27.25 (9.14)	<b>0.005</b>
VCDR	0.87 (0.11)	0.86 (0.12)	0.87 (0.13)	0.3
Visual field MD, dB	-16.87 (9.04)	-16.12 (9.15)	-16.91 (9.25)	0.2
Incisional surgery* (%)	151 (39.8)	507 (43.7)	186 (49.5)	<b>0.03</b>
Bilateral incisional surgery* rate (%)	65 (17.2)	259 (22.3)	100 (26.6)	<b>0.007</b>

Low risk group represents the first quintile of the IOP genetic risk score and the high risk is the highest quintile. Values displayed are mean (standard deviation) for continuous variables and N (%) for categorical variables. P values represent the statistical significance of the analysis of variance (difference between any two groups) for continuous variables (Kruskal–Wallis test) or Chi-squared test for categorical variables. HTG is defined by a maximum IOP >21 mmHg.

HTG: High tension glaucoma; IOP: intraocular pressure; VCDR: vertical cup-to-disc ratio; MD: mean deviation.

\* The majority of the incisional surgeries in this dataset were trabeculectomies. Other surgeries include tube shunt surgery, deep sclerectomy and two cases of Xen Gel implants .

**Table 2:** Summary of the glaucoma phenotype across genetic risk groups in the replication cohort (PROGRESSA)

Variable	Low	Intermediate	High	p
Number	144	378	102	-
Gender, male	68 (47.2)	159 (42.1)	37 (36.3)	0.228
Number of family members affected	0.60 (1.21)	0.88 (1.19)	1.27 (1.81)	<b>0.001</b>
Maximum recorded IOP, mmHg	19.31 (5.36)	21.08 (5.80)	21.03 (5.20)	<b>&lt;0.001</b>
VCDR	0.73 (0.10)	0.74 (0.10)	0.72 (0.10)	0.119
Visual field MD, dB	-3.17 (2.94)	-3.35 (3.10)	-2.79 (2.73)	0.442
Number of glaucoma drops or SLT*	1.06 (1.18)	1.36 (1.35)	1.35 (1.26)	<b>0.033</b>
Required 2 or more medications or SLT*	33 (22.9)	133 (35.2)	39 (38.2)	<b>0.013</b>

Risk group stratification is based on IOP genetic risk score cut-offs as calculated and used in the primary cohort (ANZRAG). Values displayed are mean (standard deviation) for continuous variables and N (%) for categorical variables. P values represent the statistical significance of the analysis of variance for continuous variables (Kruskal–Wallis test) or Chi-squared test for categorical variables.

\* SLT was counted as equivalent to 1 glaucoma medication.

IOP: intraocular pressure; VCDR: vertical cup-to-disc ratio; MD: mean deviation; SLT: selective laser trabeculoplasty.

Supplemental Table 1

SNP	A1	A2	BETA	SE	P
rs10918274	T	C	0.3327	0.0192	3.68E-67
rs9913911	A	G	0.2122	0.0132	2.16E-58
rs10281637	T	C	-0.2235	0.0141	6.75E-57
rs2472493	A	G	-0.1914	0.0127	3.02E-51
rs9853115	A	T	-0.1786	0.0128	1.80E-44
rs1044864	A	G	-0.2145	0.0169	7.82E-37
rs28500712	A	G	0.1791	0.0145	5.70E-35
rs12377624	C	G	-0.1542	0.013	1.23E-32
rs2022945	A	G	-0.2146	0.0188	2.49E-30
rs1579050	A	G	-0.1346	0.0127	3.90E-26
rs7123436	A	G	0.1568	0.0158	2.60E-23
rs11217863	A	G	0.1966	0.0199	4.76E-23
rs2745572	A	G	0.1329	0.0137	3.57E-22
rs55892100	A	G	0.1296	0.0134	4.37E-22
rs28470731	T	C	-0.1182	0.0128	2.55E-20
rs4775427	T	C	0.1096	0.0126	2.88E-18
rs9405157	T	C	0.1371	0.0158	4.69E-18
rs10838681	A	G	0.1225	0.0142	4.82E-18
rs4496939	A	G	-0.1155	0.0136	2.01E-17
rs9608740	A	C	-0.147	0.0174	2.41E-17
rs17687006	T	C	-0.1239	0.0147	4.06E-17
rs6478750	T	C	0.1098	0.0131	4.68E-17
rs34952318	A	G	-0.2669	0.0322	1.16E-16
rs9494457	A	T	-0.1076	0.0131	2.35E-16
rs12147852	A	G	-0.1218	0.0149	3.44E-16
rs10819187	A	G	-0.1581	0.0195	4.55E-16
rs1001989	T	C	0.1072	0.0132	4.93E-16
rs11795066	A	G	0.1035	0.0129	9.76E-16
rs4141194	A	C	0.1137	0.0142	9.94E-16
rs11651314	T	C	0.1482	0.0187	2.36E-15
rs7924522	A	C	0.1055	0.0134	3.10E-15
rs141377403	C	G	-0.4773	0.0607	3.62E-15
rs62520914	A	G	0.199	0.0253	4.17E-15
rs6781336	A	G	0.1056	0.0135	6.37E-15
rs4133395	T	G	-0.099	0.0129	1.86E-14
rs746491	A	C	0.1214	0.0158	1.90E-14
rs2279948	A	G	0.17	0.0224	3.65E-14
rs1874458	A	G	-0.0984	0.0131	7.29E-14
rs1558225	A	G	-0.116	0.0156	1.06E-13
rs78447765	T	C	-0.1776	0.0242	2.00E-13
rs12444539	A	T	-0.1755	0.0239	2.21E-13
rs31918	T	C	-0.1004	0.0139	4.54E-13
rs3743860	T	C	0.0974	0.0135	5.63E-13
rs76020419	T	G	-0.2591	0.036	6.10E-13
rs13109331	T	G	0.1131	0.0158	7.37E-13
rs7338461	A	G	0.0896	0.0125	8.22E-13
rs35705029	A	T	-0.0979	0.0138	1.20E-12

rs73111535	A	C	-0.1847	0.026	1.21E-12
rs10800149	A	C	0.0946	0.0133	1.27E-12
rs113985657	T	C	0.1272	0.0179	1.28E-12
rs7951180	A	G	0.1038	0.0146	1.30E-12
rs5756813	T	G	-0.0899	0.0128	2.25E-12
rs3778523	T	C	0.0964	0.0138	2.46E-12
rs756481	A	G	0.2062	0.0296	3.14E-12
rs10852918	A	G	-0.0892	0.0129	4.31E-12
rs4959631	T	C	-0.089	0.0129	5.95E-12
rs12413181	A	G	0.1527	0.0222	6.58E-12
rs113845710	C	G	0.1188	0.0174	7.61E-12
rs327716	A	G	0.0865	0.0127	1.04E-11
rs6546486	A	T	-0.0863	0.0128	1.38E-11
rs12045227	A	G	0.1063	0.0158	1.61E-11
rs4836547	C	G	-0.0823	0.0123	1.89E-11
rs77064891	T	C	0.3133	0.0467	1.99E-11
rs4434990	A	G	0.1283	0.0191	2.04E-11
rs7936821	C	G	-0.1258	0.0188	2.34E-11
rs67943620	A	G	0.1157	0.0177	6.23E-11
rs66724425	T	C	-0.0942	0.0145	7.72E-11
rs1501086	A	T	-0.1141	0.0176	8.29E-11
rs11752730	C	G	0.085	0.0131	8.89E-11
rs113542380	A	G	0.1596	0.0246	9.55E-11
rs4955665	T	C	0.0842	0.013	9.85E-11
rs73506198	T	C	-0.1449	0.0225	1.10E-10
rs7534738	A	C	0.0846	0.0131	1.15E-10
rs1755056	A	C	-0.0863	0.0134	1.21E-10
rs2188836	T	C	0.0831	0.0129	1.35E-10
rs72902139	T	C	-0.1388	0.0216	1.36E-10
rs1746483	C	G	0.0807	0.0127	1.80E-10
rs3013274	A	G	-0.0834	0.0131	1.81E-10
rs28613932	A	G	-0.0804	0.0126	1.82E-10
rs61755579	T	C	-0.2441	0.0383	1.94E-10
rs147699531	T	G	0.1303	0.0205	2.00E-10
rs8176747	C	G	-0.1628	0.0258	2.75E-10
rs73191227	A	G	-0.17	0.027	3.16E-10
rs12123086	A	G	-0.1238	0.0197	3.49E-10
rs1970719	T	C	-0.1203	0.0192	3.97E-10
rs1633715	T	C	0.19	0.0305	4.70E-10
rs16837021	T	C	-0.0944	0.0152	4.99E-10
rs76945759	A	G	-0.1487	0.024	5.45E-10
rs35174414	T	C	-0.0791	0.0128	7.12E-10
rs715338	A	G	-0.0797	0.013	7.73E-10
rs4672075	C	G	-0.0757	0.0124	1.12E-09
rs16856911	C	G	0.1716	0.0282	1.21E-09
rs113968938	T	C	-0.1009	0.0166	1.30E-09
rs4074961	T	C	0.0784	0.0129	1.30E-09
rs4629237	A	C	0.0797	0.0131	1.30E-09
rs73220177	A	G	-0.1512	0.0252	1.87E-09
rs11530907	C	G	0.1199	0.02	2.08E-09
rs760444	A	G	-0.0954	0.0159	2.10E-09
rs10820755	A	C	0.0788	0.0133	3.07E-09
rs35381200	T	C	-0.0772	0.013	3.10E-09
rs57435966	T	C	-0.1318	0.0223	3.65E-09
rs11065979	T	C	-0.0779	0.0132	3.98E-09

rs12356830	T	C	0.0799	0.0136	4.02E-09
rs150329092	A	G	0.2168	0.0369	4.36E-09
rs60147425	A	G	0.2881	0.0491	4.44E-09
rs111307712	T	C	-0.1167	0.0199	4.79E-09
rs3791979	T	C	-0.0788	0.0135	4.91E-09
rs2163870	A	G	0.0741	0.0127	6.15E-09
rs3134954	T	C	0.1057	0.0182	6.74E-09
rs4627617	A	G	-0.0975	0.0168	6.93E-09
rs11079868	A	G	-0.0742	0.0128	7.16E-09
rs2048047	T	C	0.0866	0.015	7.16E-09
rs10043368	A	G	-0.0732	0.0127	7.70E-09
rs4132172	T	C	-0.0833	0.0145	8.40E-09
rs10869665	T	C	-0.0815	0.0142	9.90E-09
rs2226566	A	T	0.0932	0.0163	9.92E-09
rs6095946	T	C	-0.075	0.0131	1.01E-08
rs2294239	A	G	0.0739	0.0129	1.06E-08
rs7519368	A	T	-0.0815	0.0143	1.09E-08
rs35638741	A	C	0.0733	0.0129	1.20E-08
rs6554074	T	G	-0.0708	0.0124	1.21E-08
rs11242708	T	C	-0.1036	0.0182	1.23E-08
rs9463095	A	G	0.1023	0.018	1.32E-08
rs10185855	A	G	0.0727	0.0129	1.51E-08
rs73296215	T	C	0.3162	0.0561	1.69E-08
rs72959706	A	G	0.1384	0.0246	1.89E-08
rs59427698	A	G	-0.0823	0.0146	1.90E-08
rs6065171	T	C	0.0709	0.0126	1.91E-08
rs1381486	T	G	-0.1498	0.0267	2.00E-08
rs6952464	T	C	-0.0751	0.0134	2.05E-08
rs2071280	C	G	0.0892	0.0159	2.09E-08
rs163524	A	C	0.0935	0.0167	2.11E-08
rs12786875	A	G	0.0824	0.0147	2.18E-08
rs883245	A	G	0.0736	0.0132	2.53E-08
rs10767734	T	C	0.0724	0.013	2.73E-08
rs41506447	T	G	-0.0983	0.0177	2.91E-08
rs72670480	A	G	0.092	0.0166	3.23E-08
rs215543	A	G	-0.0846	0.0154	3.91E-08
rs76778164	A	C	0.0917	0.0167	4.03E-08
rs9419741	A	G	-0.0723	0.0132	4.27E-08
rs10901553	A	G	0.0995	0.0182	4.30E-08
rs6476827	C	G	-0.0743	0.0136	4.33E-08
rs59702603	A	G	-0.1739	0.0318	4.50E-08
rs12548673	A	C	-0.0776	0.0142	4.81E-08
rs56401620	A	G	0.0973	0.0178	4.86E-08
rs56152426	A	G	0.0935	0.0171	4.99E-08